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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/506,301	12/16/2004	Ganapathy Gopalrathnam	X-15199	3398

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EXAMINER	
BARNHART, LORA ELIZABETH	
ART UNIT	**PAPER NUMBER**
1651	

DATE MAILED: 06/06/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/506,301	GOPALRATHNAM ET AL.	
	Examiner	Art Unit	
	Lora E. Barnhart	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 April 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9 and 11-24* is/are pending in the application.

4a) Of the above claim(s) *20-23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,11-19 and 24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendments

Applicant's amendments filed 4/6/06 to claims 2, 9, 14, and 24 have been entered. Claim 10 has been cancelled. Claims 1-9, 11-20, and 21-24 remain pending in the current application, of which claims 1-9, 11-19, and 24 have been considered on the merits.

Claim Objections

The objections to the claims are withdrawn in light of the claim amendments.

Claim Rejections - 35 USC § 112

The rejections under 35 U.S.C. § 112, second paragraph, are withdrawn in light of the claim amendments.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-9 and 11-19 remain rejected under 35 U.S.C. 102(b) as being anticipated by Carlson et al. (2000, U.S. Patent 6,159,468; IDS reference AU) taken in light of Voet et al. (1995, *Biochemistry*, 2nd ed.; reference U). The claims are drawn to a pharmaceutical composition comprising activated protein C and a chelating agent. In some dependent claims, the composition is lyophilized; further comprises a bulking agent, which may be selected from a list; further comprises a buffer selected from a list,

which may provide a specific pH; further comprises a salt, which may be selected from a list; or further comprises a diluent, which may have particular properties.

Carlson et al. teach a composition comprising human protein C, 0.4M sodium chloride, and 20mM Tris-acetate, pH 6.5 (Preparation 1); Preparation 1 is made 5mM in EDTA and passed over a thrombin column, thus activating protein C, and eluted with Tris buffer and lyophilized (Preparation 2). Preparation 2 therefore comprises activated protein C, EDTA (a chelator; see column 7, lines 1-2), Tris-acetate, and sodium chloride at pH 6.5 (column 7, lines 26-27; Example 1). Carlson et al. further teach dissolving lyophilized Preparation 2 in phosphate buffer, then adding a bulking agent (either mannitol, sucrose, trehalose, or raffinose) and re-lyophilizing (Examples 1 and 2).

Applicants allege that the composition of Carlson et al. is not a pharmaceutical composition because it comprises leached thrombin (Remarks, page 6, paragraph 2). Applicants further allege that Preparation 2 of Carlson et al. does not contain EDTA (Remarks, page 6, paragraph 3). These arguments have been fully considered, but they are not persuasive.

Applicants appear to have misinterpreted the teachings of Carlson et al. The text beginning at column 7, line 1, of Carlson et al. is reproduced below (**emphasis** added):

> **Purified r-hPC was made 5 mM in EDTA** (to chelate any residual calcium) and diluted to a concentration of 2 mg/mL with 20 mM Tris, pH 7.4 or 20 mM Tris-acetate, pH 6.5. This material was passed through a thrombin column equilibrated at 37.degree. C. with 50 mM NaCl and either 20 mM Tris pH 7.4 or 20 mM Tris-acetate pH 6.5. The flow rate was adjusted to allow for approximately 20 min. of contact time between the r-hPC and thrombin resin. The effluent was collected and immediately assayed for amidolytic activity. If the material did not have a specific activity (amidolytic) comparable to an established standard of aPC, it was recycled over the thrombin column **to activate the r-hPC to completion**. This was followed by 1:1 dilution of the

material with 20 mM buffer as above, with a pH of either 7.4 or 6.5 to keep the aPC at lower concentrations while it awaited the next processing step.

Removal of leached thrombin from the aPC material was accomplished by binding the aPC to an **anion exchange resin** (Fast Flow Q, Pharmacia) equilibrated in activation buffer (either 20 mM Tris, pH 7.4 or 20 mM Tris-acetate, pH 6.5) with 150 mM NaCl. Thrombin does not interact with the anion exchange resin under these conditions, but passes through the column into the sample application effluent. Once the aPC is loaded onto the column, a 2-6 column volume wash with 20 mM equilibration buffer is done before eluting the bound aPC with a **step elution using 0.4 M NaCl in either 5 mM Tris-acetate, pH 6.5 or 20 mM Tris, pH 7.4.** Higher volume washes of the column facilitated more complete removal of the dodecapeptide. The material eluted from this column was stored either in a frozen solution (-20°C) or **as a lyophilized powder** (column 7, lines 1-31).

To summarize, Carlson et al. teach combining r-hPC (recombinant human protein C) with EDTA and Tris and passing this composition over a thrombin column to activate the r-hPC; removing any thrombin with an anion exchange column; eluting with Tris-acetate and Tris; and lyophilizing the eluate, which comprises activated hPC, Tris buffer, salt, and EDTA.

Applicants' reference to "leached thrombin" is noted, but the examiner points out that this phrase is recited at column 7, line 17, of Carlson et al., within a sentence that refers to a method of **removing** thrombin from the composition. Indeed, Carlson et al. specifically state that their composition is a pharmaceutical composition: "[the improved formulations of activated protein C of the invention] are suitable for administration to a patient in need thereof" (column 2, lines 4-9).

Furthermore, applicants' assertion that "the mixture containing the leached thrombin and EDTA passes thru the column and are discarded [*sic*]" at page 6, paragraph 3, of the remarks is also incorrect. Carlson et al. teach that thrombin passes through anion exchange resin (column 7, lines 21-23); however, Voet et al. (reference

U) is cited solely as evidence that polyanions such as EDTA (ethylenediamine tetraacetate) reversibly bind to anion exchangers and do not, in fact, flow through (page 78, column 2, section A, paragraph 1). Note that the inclusion of Voet et al. herein does not create a new ground of rejection; if the examiner adds a reference in the Office action after applicant's rebuttal, and the newly added reference is added only as directly corresponding evidence to support the prior common knowledge finding, and it does not result in a new issue or constitute a new ground of rejection, the Office action may be made final. See M.P.E.P. § 2144.03 (D).

Claims 1, 9, and 11-13 remain rejected under 35 U.S.C. 102(b) as being anticipated by Foster et al. (1996, U.S. Patent 5,516,650; IDS reference AO) taken in light of Carlson et al. (AU). The claim is drawn to a pharmaceutical composition comprising activated protein C and a chelating agent. In some claims, the composition further comprises a diluent.

Foster et al. teach a solution comprising activated protein C, EDTA (a chelating agent), and TBS (Tris-buffered saline) in water (column 21, lines 20-24). Carlson et al. is cited as evidence that Tris is a pharmaceutically acceptable buffer (column 3, lines 9-12).

Applicants allege that Foster et al. do not "teach or suggest that EDTA could be used in an aPC [activated protein C] formulation or that the eluent from the antibody column could be used as a pharmaceutical composition" (Remarks, page 7, paragraph 3). Applicants further allege that Foster et al. "recognized that additional purification of [the eluate of the invention] would be required" (*ibid.*), citing column 9, lines 48-50 of

Foster et al. Applicants allege that "one skilled in the art would recognize that this eluent from the monoclonal antibody purification column would not be acceptable for pharmaceutical administration to humans" (*ibid.*). These arguments have been fully considered, but they are not persuasive.

Contrary to applicants' assertions, Foster et al. specifically contemplate the use of their compositions as pharmaceuticals: "The proteins described within the present invention may be used as active therapeutic substances, including use in the regulation of blood coagulation" (column 4, lines 1-3). Applicants provide no evidence that the compositions of Foster et al. are unacceptable for human consumption; these assertions have been treated as attorney argument. Attorney argument is not evidence unless it is an admission, in which case, an examiner may use the admission in making a rejection. See M.P.E.P. § 2129 and § 2144.03 for a discussion of admissions as prior art. Counsel's arguments cannot take the place of objective evidence. *In re Schulze*, 145 USPQ 716 (CCPA 1965); *In re Cole*, 140 USPQ 230 (CCPA 1964); and especially *In re Langer*, 183 USPQ 288 (CCPA 1974). See M.P.E.P. § 716.01(c) for examples of attorney statements that are not evidence and that must be supported by an appropriate affidavit or declaration.

At column 21, line 24, Foster et al. teach, "protein C was eluted with TBS containing 10mM EDTA." In subsequent paragraphs, Foster et al. detail various measurements conducted on the composition produced in column 21, line 24 (column 21, line 27, through column 22, line 8). The fact that Foster et al. contemplate further purification at column 9 (a section not comprised within the working Examples cited by

the Examiner) is not evidence that the composition of column 21, line 24, is unacceptable for administration as a pharmaceutical composition. In light of Foster et al.'s statement of asserted utility at column 4, lines 1-3, the person of ordinary skill in the art would expect that the composition of column 21, line 24, is a pharmaceutically acceptable composition.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-9, 11-19, and 24 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Carlson et al. (2000, U.S. Patent 6,159,468; IDS reference AU). The claims are drawn to a pharmaceutical composition comprising activated protein C and a chelating agent. In some dependent claims, the composition is lyophilized; further comprises a bulking agent, which may be selected from a list; further comprises a buffer selected from a list, which may provide a specific pH; further comprises a salt, which

may be selected from a list; or further comprises a diluent, which may have particular properties.

As discussed above, Carlson et al. teach a composition comprising human protein C, 0.4M sodium chloride, and 20mM Tris-acetate, pH 6.5 (Preparation 1); Preparation 1 is made 5mM in EDTA and passed over a thrombin column, thus activating protein C, and eluted with Tris buffer and lyophilized (Preparation 2). Preparation 2 therefore comprises activated protein C, EDTA (a chelator; see column 7, lines 1-2), Tris-acetate, and sodium chloride at pH 6.5 (column 7, lines 26-27; Example 1). Carlson et al. further teach dissolving lyophilized Preparation 2 in phosphate buffer, then adding a bulking agent (either mannitol, sucrose, trehalose, or raffinose) and re-lyophilizing (Examples 1 and 2). Carlson et al. do not exemplify other buffers or salts.

Carlson et al. teach that mannitol, trehalose, raffinose, and sucrose are all acceptable bulking agents for the composition (column 3, lines 29-30 and 60-63). Carlson et al. further teach that Tris buffers, citrate buffers, phosphate buffers, and acetate buffers are all pharmaceutically acceptable buffers (column 3, lines 9-12, and column 4, lines 20-27). Carlson et al. teach that the pH of the composition, upon reconstitution, is between 5.5 and 6.5 (column 3, lines 30-33). Carlson et al. further teach that potassium chloride and sodium chloride are acceptable salts for inclusion in the composition (column 4, lines 37-41). Carlson et al. teach the importance of removal of residual calcium using chelators, for example EDTA, from protein C preparations (column 6, lines 35-50). Finally, Carlson et al. contemplate the administration of the composition to a patient in need thereof (column 5, lines 38-58).

The selection of bulking agent, salt, and buffer from among the recited species clearly would have been a routine matter of optimization on the part of the artisan of ordinary skill, said artisan recognizing that Carlson et al. teach that said species are acceptable substitutes for each other (see above). A holding of obviousness over the cited claims is therefore clearly required.

While the composition of Carlson et al. comprises some EDTA from the activation step (column 7, lines 1-3), **a person of ordinary skill in the art would have had a reasonable expectation of success in including additional EDTA in the composition of Carlson et al. because EDTA is taught by Carlson et al. not to affect the composition's essential properties. The skilled artisan would have been motivated to include additional EDTA for the expected benefit that activated protein C would be protected from calcium and other divalent ions.** It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was made to include additional EDTA in the composition of Carlson et al. because Carlson et al. suggest its inclusion to chelate metal ions.

Therefore, the invention as a whole would have been *prima facie* obvious to a person of ordinary skill at the time the invention was made.

Applicants allege, "there is no evidence that the skilled artisan would have been motivated to modify [Carlson et al.] or more importantly that Applicants' modifications would have a reasonable expectation of success [*sic*]" (Remarks, page 9, paragraph 2). Applicants further allege that "they discovered that the addition of a chelating agent with the diluent used with the aPC formulation or to the aPC formulation itself improves the

solution stability of aPC" and that Carlson et al. fails to teach this effect (Remarks, page 10, paragraph 3). Applicants allege that the Examiner "identifies no suggestion or incentive in Carlson et al. that would have motivated the skilled artisan to protein C to add a chelating agent to the diluent used with the aPC formulation or to the aPC formulation itself to improve the solution stability of aPC [*sic*]" (*ibid.*). Applicant requests that the Examiner "substantiate this allegation [rejection] with sound reasoning or evidence" (Remarks, page 9, paragraph 4). These arguments have been fully considered, but they are not persuasive.

The examiner pointed out in the first Office action that the person of ordinary skill in the art would have had both a reasonable expectation of success in modifying the teachings of Carlson et al. and a motivation to do so at the time of the invention on the first Office action; these assertions have herein been placed in **bold** for applicant's convenience. The standard for obviousness is that the prior art must *suggest* a motivation to modify (as Carlson et al. does: EDTA secludes calcium from protein C, allowing the protein's activation; column 6, lines 35-49), not that the prior art must include "an express written motivation" for modification. *Ruiz v. A.B. Chance Co.*, 357 F.3d 1270, 69 USPQ2d 1686 (Fed. Cir. 2004) at 1690.

Applicants' alleged finding of unexpected results is unpersuasive for two reasons. First, the claims do not recite or imply that the composition must have "improved solution stability;" this argument is, therefore, directed to limitations not recited in the claims and is, therefore, ineffective. See M.P.E.P. § 2145 (VI). Although the claims are

interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Even if a limitation regarding "solution stability" were placed into the claims, applicants have failed to meet the standard for a showing of unexpected results. Applicants have provided no substantive evidence that the addition of a chelating agent to the diluent used with the aPC formulation or to the aPC formulation itself results in any patentable difference in the composition compared to that of Carlson et al. Objective evidence which must be factually supported by an appropriate affidavit or declaration to be of probative value includes evidence of unexpected results. See, for example, *In re De Blauwe*, 736 F.2d 699, 705, 222 USPQ 191, 196 (Fed. Cir. 1984), in which the CAFC wrote, "It is well settled that unexpected results must be established by factual evidence." See M.P.E.P. § 716.01(c) (I). The instant allegation of unexpected results is merely the argument of counsel and is unsupported by evidence or declarations of those skilled in the art. Attorney argument is not evidence unless it is an admission, as discussed above in the rejection under §102(b) over Foster et al. taken in light of Carlson et al.

No claims are allowed. No claims are free of the art.

Applicant should specifically point out the support for any amendments made to the disclosure, including the claims (MPEP 714.02 and 2163.06). Due to the procedure outlined in MPEP § 2163.06 for interpreting claims, it is noted that other art may be applicable under 35 U.S.C. § 102 or 35 U.S.C. § 103(a) once the aforementioned issue(s) is/are addressed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lora E. Barnhart whose telephone number is 571-272-1928. The examiner can normally be reached on Monday-Friday, 8:00am - 4:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Lora E Barnhart

LEB

SANDRA E. SAUCIER
PRIMARY EXAMINER